

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Division of Patent Application Serial No. 09/533,381 of

FANTO et al

Atty. Ref.: 2801-36

Serial No. to be assigned

Group: 1621

Filed: March 26, 2001

Examiner: Barts

For: 2-AMINOTETRALINES AND PHARMACEUTICAL COMPOSITIONS FOR THE  
PREVENTION AND THERAPEUTIC TREATMENT OF INFLAMMATORY  
AND/OR AUTOIMMUNE PATHOLOGIES

\* \* \* \* \*

March 26, 2001

Assistant Commissioner for Patents  
Washington, DC 20231

Sir:

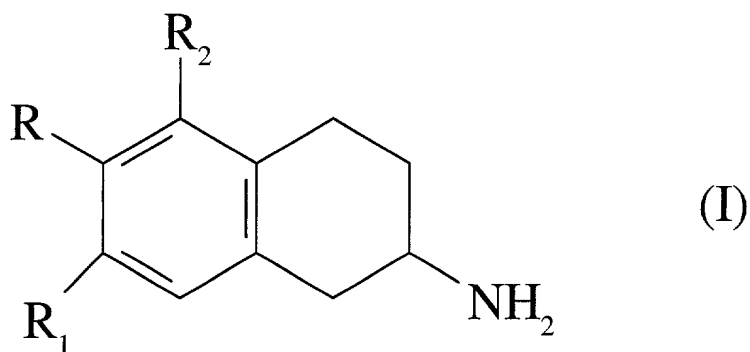
**PRELIMINARY AMENDMENT**

In order to place the above-identified application in better condition for  
examination, please amend the application as follows:

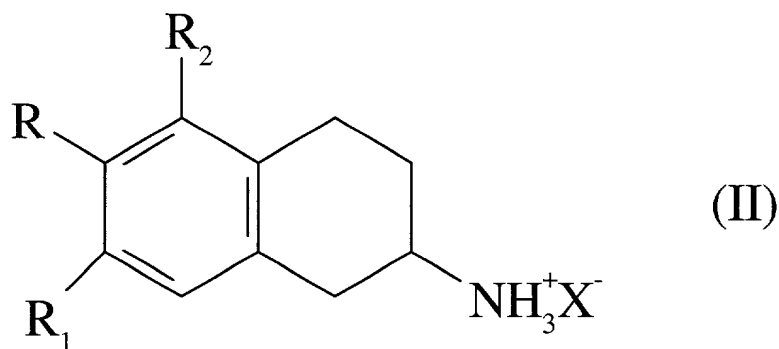
**IN THE CLAIMS**

Cancel claims 1-7 and add the following new claims

8. A method of treating an inflammatory and/or autoimmune pathology induced  
by inflammatory cytokines, which method comprises administering to a patient in need of  
same an effective amount of a 2-aminotetraline of the formula (I)



or a pharmacologically acceptable salt of the formula (II)



wherein:

R and R<sub>1</sub> are independently halogen, hydroxy, or C<sub>1</sub>-C<sub>4</sub> alkoxy optionally substituted in position ω with a group selected from OH, NH<sub>2</sub> or NR<sub>3</sub>R<sub>4</sub>, wherein R<sub>3</sub> and R<sub>4</sub> are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, unsubstituted or substituted in position ω with groups OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkanoyl, C<sub>1</sub>-C<sub>4</sub> alkyl, carbamoyl, carbamoyloxy, amino, or amino-substituted NR<sub>3</sub>R<sub>4</sub>, where R<sub>3</sub> and R<sub>4</sub> have the above meanings,

$R_2$  is hydrogen, halogen, hydroxy or methoxy,

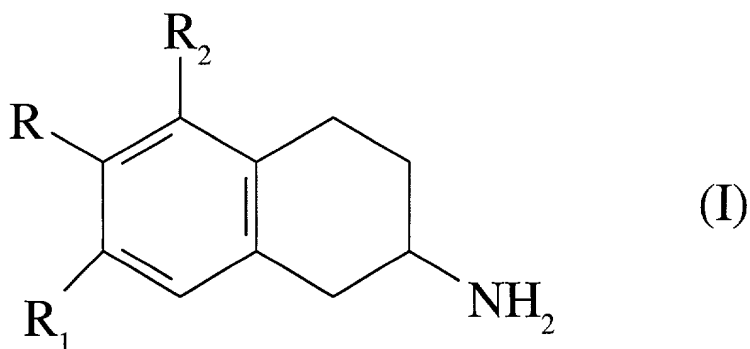
with the proviso that the 2-aminotetraline excludes (a)  $R=R_1=CH_3O$  or  $OH$ ,  $R_2=H$ ,

(b)  $R=F$ ,  $R_1=CH_3O$  or  $OH$ ,  $R_2=H$ , (c)  $R_1=-OCH_3$ ,  $R=CH_3$  and  $R_2=H$ , or (d)

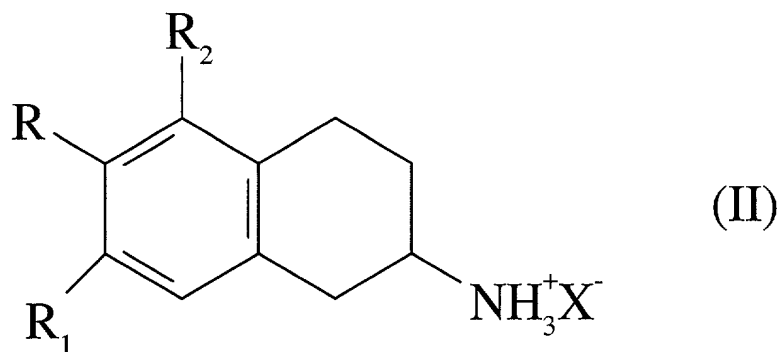
$R=R_1=R_2=CH_3O$ ,

and  $X^-$  is the monovalent anion of a pharmacologically acceptable acid.

9. A method of preventing or treating septic shock comprising administering to a patient in need of same an effective amount of a 2-aminotetraline of the formula (I)



or a pharmacologically acceptable salt of the formula (II)



wherein:

R and R<sub>1</sub> are independently halogen, hydroxy, or C<sub>1</sub>-C<sub>4</sub> alkoxy optionally substituted in position ω with a group selected from OH, NH<sub>2</sub> or NR<sub>3</sub>R<sub>4</sub>, wherein R<sub>3</sub> and R<sub>4</sub> are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, unsubstituted or substituted in position ω with groups OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkanoyl, C<sub>1</sub>-C<sub>4</sub> alkyl, carbamoyl, carbamoyloxy, amino, or amino-substituted NR<sub>3</sub>R<sub>4</sub>, where R<sub>3</sub> and R<sub>4</sub> have the above meanings,

R<sub>2</sub> is hydrogen, halogen, hydroxy or methoxy,

with the proviso that the 2-aminotetraline excludes (a) R=R<sub>1</sub>=CH<sub>3</sub>O or OH, R<sub>2</sub>=H,

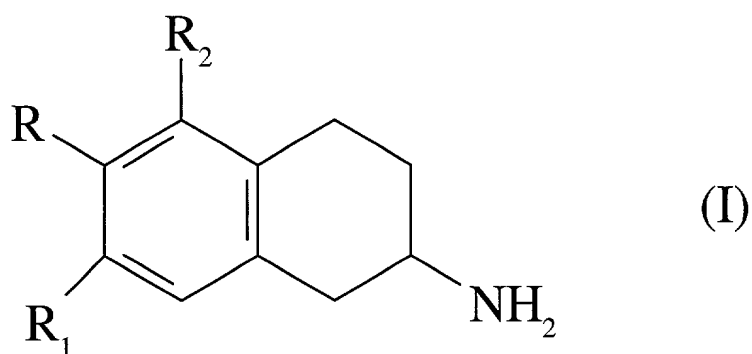
(b) R=F, R<sub>1</sub>=CH<sub>3</sub>O or OH, R<sub>2</sub>=H, (c) R<sub>1</sub>=-OCH<sub>3</sub>, R=CH<sub>3</sub> and R<sub>2</sub>=H, or (d)

R=R<sub>1</sub>=R<sub>2</sub>=CH<sub>3</sub>O, and

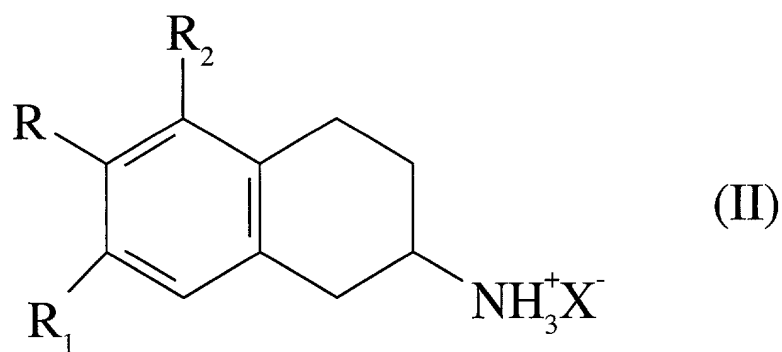
X<sup>-</sup> is the monovalent anion of a pharmacologically acceptable acid.

10. A method of treating rheumatoid arthritis, pancreatitis, inflammatory bowel disease, systemic lupus erythematosus, glomerulonephritis or encephalomyelitis,

comprising administering to a patient in need of same an effective amount of 2-aminotetraline of the formula (I)



or a pharmacologically acceptable salt of the formula (II)



wherein:

R and R<sub>1</sub> are independently halogen, hydroxy, or C<sub>1</sub>-C<sub>4</sub> alkoxy optionally substituted in position ω with a group selected from OH, NH<sub>2</sub> or NR<sub>3</sub>R<sub>4</sub>, wherein R<sub>3</sub> and R<sub>4</sub> are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, unsubstituted or substituted in position ω with

groups OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkanoyl, C<sub>1</sub>-C<sub>4</sub> alkyl, carbamoyl, carbamoyloxy, amino, or amino-substituted NR<sub>3</sub>R<sub>4</sub>, where R<sub>3</sub> and R<sub>4</sub> have the above meanings,

R<sub>2</sub> is hydrogen, halogen, hydroxy or methoxy,

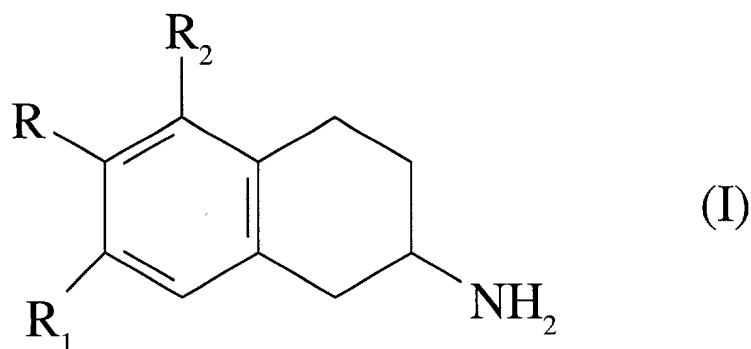
with the proviso that the 2-aminotetraline excludes (a) R=R<sub>1</sub>=CH<sub>3</sub>O or OH, R<sub>2</sub>=H,

(b) R=F, R<sub>1</sub>=CH<sub>3</sub>O or OH, R<sub>2</sub>=H, (c) R<sub>1</sub>=-OCH<sub>3</sub>, R=CH<sub>3</sub> and R<sub>2</sub>=H, or (d)

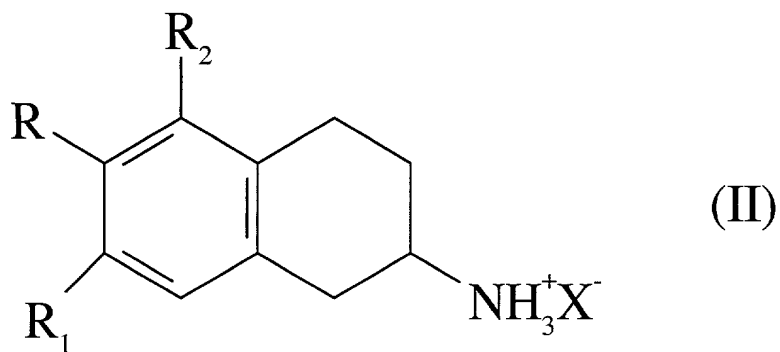
R=R<sub>1</sub>=R<sub>2</sub>=CH<sub>3</sub>O,

and X<sup>-</sup> is the monovalent anion of a pharmacologically acceptable acid.

11. A method of treating an inflammatory and/or autoimmune pathology induced by inflammatory cytokines, which method comprises administering to a patient in need of same an effective amount of a compound of the formula (I)



or a pharmacologically acceptable salt of the formula (II)



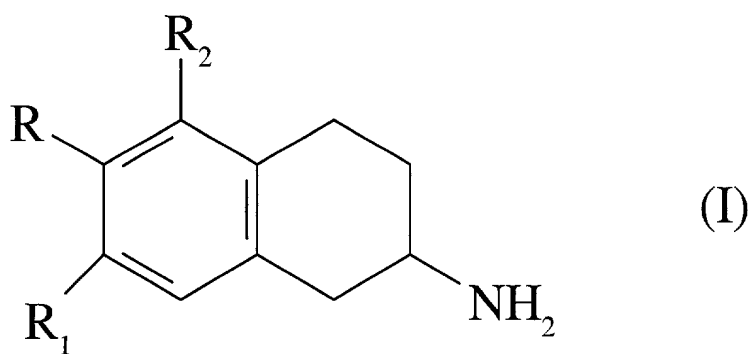
wherein:

R and R<sub>1</sub> are independently halogen, hydroxy, or C<sub>1</sub>-C<sub>4</sub> alkoxy optionally substituted in position ω with a group selected from OH, NH<sub>2</sub> or NR<sub>3</sub>R<sub>4</sub>, wherein R<sub>3</sub> and R<sub>4</sub> are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, unsubstituted or substituted in position ω with groups OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkanoyl, C<sub>1</sub>-C<sub>4</sub> alkyl, carbamoyl, carbamoyloxy, amino, or amino-substituted NR<sub>3</sub>R<sub>4</sub>, where R<sub>3</sub> and R<sub>4</sub> have the above meanings,

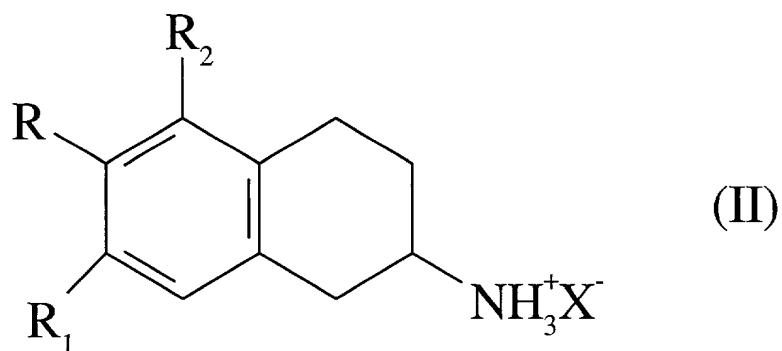
R<sub>2</sub> is hydrogen, halogen, hydroxy or methoxy, and

X<sup>-</sup> is the monovalent anion of a pharmacologically acceptable acid.

12. A method of preventing or treating septic shock comprising administering to a patient in need of same an effective amount of a compound of the formula (I)



or a pharmacologically acceptable salt of the formula (II)



wherein:

R and R<sub>1</sub> are independently halogen, hydroxy, or C<sub>1</sub>-C<sub>4</sub> alkoxy optionally substituted in position ω with a group selected from OH, NH<sub>2</sub> or NR<sub>3</sub>R<sub>4</sub>, wherein R<sub>3</sub> and

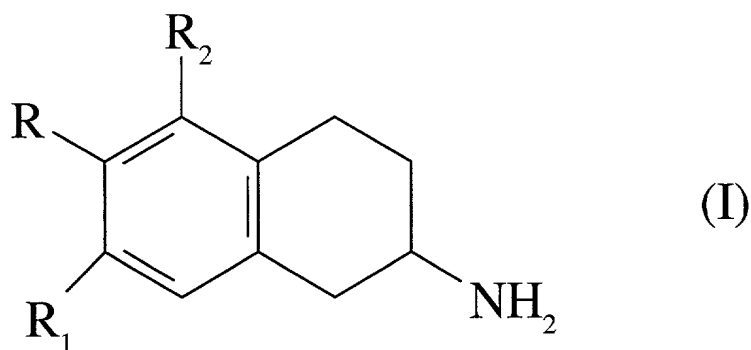


$R_4$  are independently H,  $C_1$ - $C_4$  alkyl, unsubstituted or substituted in position  $\omega$  with groups OH,  $NH_2$ ,  $C_1$ - $C_4$  alkanoyl,  $C_1$ - $C_4$  alkyl, carbamoyl, carbamoyloxy, amino, an amino-substituted  $NR_3R_4$ , where  $R_3$  and  $R_4$  have the above meanings,

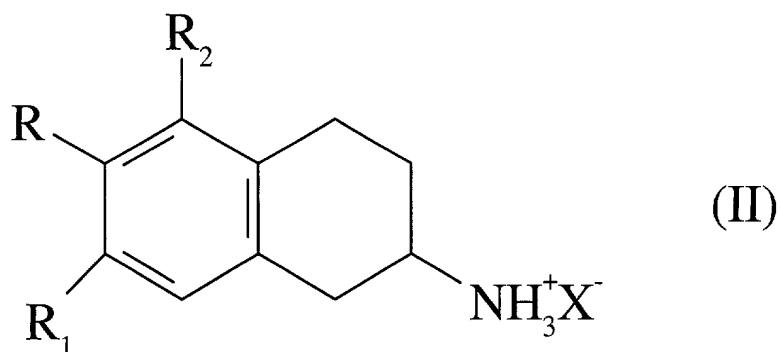
$R_2$  is hydrogen, halogen, hydroxy or methoxy, and

$X^-$  is the monovalent anion of a pharmacologically acceptable acid,  
provided that the compound where  $R=F$ ,  $R_1=-CH_3O$  and  $R_2=H$  is excluded.

13. A method of treating rheumatoid arthritis, pancreatitis, inflammatory bowel disease, systemic lupus erythematosus, glomerulonephritis or encephalomyelitis, comprising administering to a patient in need of same an effective amount of a compound of the formula (I)



or a pharmacologically acceptable salt of the formula (II)



wherein:

R and R<sub>1</sub> are independently halogen, hydroxy, or C<sub>1</sub>-C<sub>4</sub> alkoxy optionally substituted in position ω with a group selected from OH, NH<sub>2</sub> or NR<sub>3</sub>R<sub>4</sub>, wherein R<sub>3</sub> and R<sub>4</sub> are independently H, C<sub>1</sub>-C<sub>4</sub> alkyl, unsubstituted or substituted in position ω with groups OH, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkanoyl, C<sub>1</sub>-C<sub>4</sub> alkyl, carbamoyl, carbamoyloxy, amino, or amino-substituted NR<sub>3</sub>R<sub>4</sub>, where R<sub>3</sub> and R<sub>4</sub> have the above meanings,

R<sub>2</sub> is hydrogen, halogen, hydroxy or methoxy, and

X<sup>-</sup> is the monovalent anion of a pharmacologically acceptable acid.

14. A method of treating an inflammatory and/or autoimmune pathology induced by inflammatory cytokines, which method comprises administering to a patient in need of same an effective amount of a compound selected from the group consisting of:

S(-)-2-amino-6-fluoro-7-hydroxytetraline hydrochloride;

R(+)-2-amino-6-fluoro-7-hydroxytetraline hydrochloride;

(R,S)-2-amino-5,6-difluoro-7-methoxytetraline hydrochloride;

(R,S)-2-amino-6-fluoro-7-methyltetraline hydrochloride;  
(R,S)-2-amino-7-fluoro-6-hydroxytetraline hydrochloride;  
(R,S)-7-acetyl-2-amino-6-methyltetraline hydrochloride; and  
(R,S)-2-amino-7-fluoro-6-methoxytetraline hydrochloride.

15. A method of preventing or treating septic shock comprising administering to a patient in need of same an effective amount of a compound selected from the group consisting of:

S(-)-2-amino-6-fluoro-7-hydroxytetraline hydrochloride;  
R(+)-2-amino-6-fluoro-7-hydroxytetraline hydrochloride;  
(R,S)-2-amino-5,6-difluoro-7-methoxytetraline hydrochloride;  
(R,S)-2-amino-6-fluoro-7-methyltetraline hydrochloride;  
(R,S)-2-amino-7-fluoro-6-hydroxytetraline hydrochloride;  
(R,S)-7-acetyl-2-amino-6-methyltetraline hydrochloride; and  
(R,S)-2-amino-7-fluoro-6-methoxytetraline hydrochloride.

16. A method of treating rheumatoid arthritis, pancreatitis, inflammatory bowel disease, systemic lupus erythematosus, glomerulonephritis or encephalomyelitis, comprising administering to a patient in need of same an effective amount of a compound selected from the group consisting of:

S(-)-2-amino-6-fluoro-7-hydroxytetraline hydrochloride;  
R(+)-2-amino-6-fluoro-7-hydroxytetraline hydrochloride;  
(R,S)-2-amino-5,6-difluoro-7-methoxytetraline hydrochloride;  
(R,S)-2-amino-6-fluoro-7-methyltetraline hydrochloride;

(R,S)-2-amino-7-fluoro-6-hydroxytetraline hydrochloride;  
(R,S)-7-acetyl-2-amino-6-methyltetraline hydrochloride; and  
(R,S)-2-amino-7-fluoro-6-methoxytetraline hydrochloride. —

Attached: Abstract

**REMARKS**

This application is a division of Serial No. 09/533,381 filed March 22, 2000.

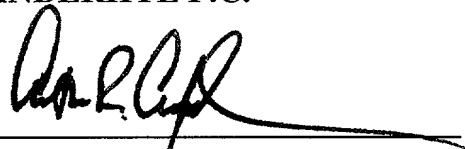
During the examination of that application claims were added directed to methods of treatment. Original claim 7 was cast in a European-style method of treatment but not correctly treated on the merits in the parent application. In an Official Action of January 18, 2001, paper No. 5, these claims were withdrawn from consideration as not directed to the subject matter previously examined.

Please examine the above claims taking into account the documents of record in the parent case to the extent they may pertain.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

By: \_\_\_\_\_



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## **ABSTRACT**

2-Aminotetralines, a process for their preparation, and pharmaceutical compositions, for the prevention and therapeutic treatment of inflammatory pathologies (particularly septic shock) and/or autoimmune pathologies in which the aetiopathogenic role of inflammatory cytokines has been ascertained.